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(54) Title: METHODS AND COMPOSITIONS FOR TREATING REWARD DEFICIENCY SYNDROME

(57) Abstract: The present invention relates to methods and compositions for treating Reward Deficiency Syndrome (RDS) using a therapeutically effective amount of a monoamine oxidase B inhibitor. The present invention also relates to compositions for treating RDS comprising selegiline in very low dose.

METHODS AND COMPOSITIONS FOR TREATING REWARD DEFICIENCY SYNDROME

TECHNICAL FIELD OF THE INVENTION

The present invention relates to methods for treating Reward Deficiency Syndrome by using a therapeutically effective amount of a monoamine oxidase B inhibitor. The present invention also relates to compositions for treating Reward Deficiency Syndrome comprising selegiline in very low dose.

BACKGROUND OF THE INVENTION

1.1 Monoamine Oxidase B Inhibitors

Monoamine oxidases (MAO) are iron containing enzymes that exist as two isozymes A (MAOA) and B (MAOB). Monoamine oxidases generate hydroxy radicals which may be involved in neurodegenerative disorders such as Parkinson's Disease. MAOA is thought to be primarily involved in the deamination of serotonin, epinephrine, norepinephrine and tyramine. MAOB is thought to be primarily involved in the deamination of dopamine and β-phenylethylamine. Some MAOB inhibitors known in the art are selegiline (Jumex®, Jumexal® Carbex®, Eldepryl®, Movergan®; Aptapryl®, Anipryl®; Eldeprine®; Plurimen®), desmethylselegiline, paragyline (Eudatin®, Supirdyl®, Eutonyl®) [U.S. patent 3,155,584], rasagiline [R(+)N-propargyl-laminoindan], 3-N-phenylacetylamino-2,5-piperidinedione and caroxyazone.

Selegiline, also known as l-deprenyl, is generally regarded as a selective MAO-B inhibitor at low doses (10mgs/day or less in humans) or a non-

selective MAO-A and MAO-B inhibitor at higher doses (e.g., Schaller, J.L. et al., J. Neuropsychiatry 9:302-301 (1997); Reiderer, P., et al., J. Neural Transmission 43:217-226 (1978); Sunderland, T., Psychopharmacol. 86:432-437 (1985)). The smallest dosage forms of selegiline on the market is believed to be 5mg tablets or capsules, which are not scored (i.e., Carbex®). The pharmacokinetics and pharmacodynamics of selegiline have been reported (e.g., Mahmood I, Clinical Pharmacokinet. 33:91-102 (1997)). Methods for preparing selegiline are known in the art (e.g., J.S. Fowler, J. Org. Chem. 42:2637 (1977); U.S. patent 4,564,706).

Clinical studies involving the administration of selegiline to humans and/or animals suffering from clinical depression, atypical depression, Parkinson's disease, Attention-Deficit/Hyperactivity Disorder, Tourette's Syndrome, Alzheimers' disease, and immune system dysfunctions have been reported. [Feigin, A., et al., Neurology 46:965-968 (1996); Quitkin, F.M., et al., Arch. Gen. Psychiatry 41:777-81 (1984); Wood, D.R., et al., Psychopharmacol. Bull. 19:627-629 (1983); Tariot, P.N. et al., Arch. Gen. Psychiatry 44:427-33 (1987); United States patent 5,387,615]

For example, United States patent 4,868,218 proposes the transdermal administration of selegiline in an amount of 5mgs to 50mgs per day for the treatment of depression. However, no clinical data is provided. Subsequent clinical studies have shown that oral administration of less than 10mgs/day is not effective at treating depression whereas administration of greater than 10mgs/day of selegiline is effective for treating depression (e.g., Kuhn, W., et al., J. Neural. Transm. Suppl. 48:85-93 (1996)).

1.2 Reward Deficiency Syndrome

Reward Deficiency Syndrome (RDS) is a disorder first described by Blum and co-workers as a form of sensory deprivation of the brain's pleasure mechanisms. [Blum, K., et al., "Reward Deficiency Syndrome," American Scientist, (March-April 1996)] Subsequent studies have proposed that RDS has a biochemical basis that manifests as an inability to derive reward from ordinary, everyday activities. Id. Patients suffering from RDS may also suffer from impulsive, compulsive or addictive disorders such as severe alcoholism, Tourette's Syndrome and Attention-Deficit Disorder. However, not all patients suffering from these impulsive, compulsive or addictive disorders also suffer from RDS.

Most, if not all, studies relating to impulsive, compulsive or addictive disorders have not investigated RDS. For example, in one study, a percentage of Attention Deficit Hyperactivity Disorder (ADHD) patients treated with a low dose of pargyline or selegiline reported improvement (Wender, P.H., J. Clin Psychiatry 59(suppl 7):76-79 (1998)). There was no indication whether any of the patients suffered from RDS. Similarly, in another study, a high percentage of children suffering from Tourette's syndrome-ADHD treated with 5 to 15 mg/day of selegiline reported improvement (Jankovic, J., Arch. Neurol. 50:386-388 (1993)). Again, there was no indication that the children suffered from RDS. Currently, there is little or no clinical data describing a treatment for RDS patients.

Researchers have suggested that the dopamine system plays a role in the processing of reward information (Schultz, W., J. Neurophysiol. 80:1-27

(1998)). For example, some studies have suggested that the A1 allele of the dopamine D2 receptor (DRD_2) may be important for the development of disorders such as alcoholism, obesity, attention deficit disorder and RDS (e.g., Blum, K., et al., Pharmacogenetics 5:121-141 (1995)). Conversely, other studies have excluded linkage of the DRD_2 gene with alcoholism (e.g., Gorman, D., et al., Alcohol 16:47-52 (1998); Suarez, B.K., et al., Genomics 19:12-20 (1994)). Still others have suggested a correlation between the dopamine D4 receptor and alcoholism and nicotine dependence (Blum, K., et al., American Scientist (March-April 1996)). Consequently, a direct link between reward processing in general and the dopamine metabolic pathway and/or RDS has yet to be established.

SUMMARY OF THE INVENTION

The present invention relates to methods and compositions for treating a patient suffering from Reward Deficiency Syndrome using a therapeutically effective amount of a monoamine oxidase B inhibitor (MAOB-I). Thus, an object of this invention is to provide a method for treating RDS by administering an amount of MAOB-I necessary to inhibit MAOB but cause little or reduced inhibition of MAOA activity. In one embodiment, the MAOB-I is selegiline administered in an amount of 10mgs/day or less per day. In a preferred embodiment, selegiline is administered in an amount of less than 10mgs/day.

Another object of this invention is to provide a composition comprising selegiline for treating RDS, which is better suited for treating RDS than the currently available dosage forms. Thus, a selegiline composition of this invention would be

prepared as a single unit comprising less than 2.5 mg of selegiline or as a unit that is pre-prepared into separable portions, each portion of which comprises less than 2.5 mg of selegiline, such that selegiline may be administered accurately and quantitatively to patients in the low dosages necessary to treat RDS. An advantage of this composition is that a practitioner may be better able to determine the appropriate dosage regimen for a patient.

DETAILED DESCRIPTION

A MAOB inhibitor according to this invention is a compound that inhibits MAOB but causes much less or no inhibition of MAOA activity or a compound that selectively inhibits MAOB (e.g., within a particular dosage range). Hereinafter, the activity of a MAOB inhibitor as used according to this invention will be referred to as "selective MAOB-I activity." In one embodiment, the MAOB inhibitor is selected from the group consisting of selegiline, desmethylselegiline, paragyline, rasagiline [R(+)N-propargyl-laminoindan], 3-N-phenylacetylamino-2,5-piperidinedione and caroxyazone. In another embodiment, the MAOB inhibitor is a derivative or metabolite of selegiline, desmethylselegiline, paragyline, rasagiline [R(+)N-propargyl-laminoindan], 3-N-phenylacetylamino-2,5-piperidinedione and caroxyazone. Said derivative or metabolite should have substantially the same or better selective MAOB-I activity as its underivatized or unmetabolized form.

A MAOB inhibitor of this invention, including selegiline, pargyline, or a derivative or metabolite thereof, as used herein may be administered in the form of a prodrug, i.e., drugs that are metabolized in vivo

into the active agent. Prodrugs useful according to this invention have substantially the same selective MAOB-I activity or better than the non-prodrug form. Methods for making prodrugs are readily known in the art (e.g., Balant, L.P., "Prodrugs for the Improvement of Drug Absorption Via Different Routes of Administration," Eur. J. Drug Metab. Pharmacokinet. 15:143-153 (1990); and Bundgaard, H., "Novel Chemical Approaches in Prodrug Design," Drugs of the Future 16:443-458 (1991); incorporated by reference herein).

The term MAOB inhibitor according to this invention, including selegiline, pargyline, or a derivative or metabolite thereof, as used herein includes pharmaceutically acceptable salts of those compounds and their prodrugs. Pharmaceutically acceptable salts of MAOB-I, selegiline or pargyline useful according to the methods of this invention are salts prepared from pharmaceutically acceptable reagents known in the art. In one preferred embodiment, said pharmaceutically acceptable salt is the hydrochloride salt of selegiline or pargyline.

Methods for evaluating the activity of monoamine oxidase B and monoamine oxidase A known in the art can be used for selecting MAOB inhibitors according to this invention. For example, blood samples may be drawn to determine platelet MAO activity using radiolabelled benzylamine or phenylethylamine. (i.e., evaluating MAOB inhibitory activity). [Murphy, D.L., et a., Psychopharm. 62:129-132 (1979); Murphy, D.L., et al., Biochem. Med. 16:254-265 (1976); all incorporated by reference herein] In one embodiment, MAOB activity should be decreased greater than 80% compared to MAOB enzyme activity before treatment. In a preferred embodiment, MAOB activity is decreased

greater than 90% or 95% compared to MAOB activity before treatment.

For example, MAOA inhibitory activity may be evaluated by measuring levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) or 5-hydroxyindoleacetic acid (5-HIAA) in the plasma of blood or in cerebral spinal fluid (CSF) by using gas chromatography-mass spectroscopy (gc-ms). [Murphy, D.L., et al., "Selective Amine Oxidase Inhibitors: Basic to Clinical Studies and Back," Clinical Pharmacology in Psychiatry, 3rd Series., Eds. Dahl, Gram, Paul, and Potter, Springer-Verlag: 1987; Major, L.F., et al., J. Neurochem. 39:229-231 (1979); Jimerson, D.C., et al., Biomed. Mass. Spectrom. 8:256-259 (1981); all incorporated by reference herein] In one embodiment, after administration of the MAOB-I, plasma MHPG levels should not be reduced lower than 45% of pretreatment levels of plasma MHPG. In a preferred embodiment, after administration of the MAOB-I, plasma MHPG or CSF 5-HIAA levels should not be reduced more than 80% of pretreatment levels of MHPG or 5-HIAA levels, respectively.

MAOB inhibitors for use in this invention may be prepared as a composition comprising a therapeutically effective amount of MAOB inhibitor and a pharmaceutically acceptable carrier.

A preferred composition according the present invention comprises a pharmaceutically acceptable carrier together with less than 2.5 mg of selegiline or a prodrug thereof, formulated into a single unit, or a unit that is pre-prepared into separable portions (hereinafter, "separable composition"), each portion of which comprises less than 2.5 mgs of selegline or a prodrug thereof. In one embodiment, the composition or

each portion of the separable composition comprises less than 2.5 mgs of selegline or a prodrug thereof. In another embodiment, the composition or each portion of the separable composition comprises less than or equal to 2 mg or 1 mg of selegline or a prodrug thereof. For example, a separable composition is a scored tablet.

A composition according the present invention may further comprise another therapeutic agent. In one embodiment of this invention, the therapeutic agent is a benzodiazepine. Benzodiazepines useful according to this invention include chlordiazepoxide, clorazepate, diazepam, flurazepam, halazepam, prazepam, alprazolam, clonazepam, flunitrazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, and triazolam.

Said therapeutic agents may be administered according to methods of this invention before, during or after the administration of the MAOB inhibitor.

"Reward Deficiency Syndrome" or RDS according to this invention is a chronic and pervasive inability or deficient ability to experience pleasure and/or comfort from ordinary daily activities that are generally emotionally-rewarding in nature. For example, patients suffering from RDS typically complain of two or more, if not all of the following: lack of satisfaction or enjoyment from work, lack of satisfaction or enjoyment from social interaction with friends or family, and lack of satisfaction or enjoyment from hobbies and interests. Individuals suffering soley from an inability to work or socialize, often associated with depression, should not be confused with RDS patients who are unable to obtain or have a reduced capacity to obtain pleasure from activities. An RDS patient will have experienced RDS

throughout his/her life, but usually acknowledges the severity of some of the symptoms of RDS as early as puberty. One hallmark of an RDS patient is the inability to complete projects or hobbies.

As a result of this inability or deficient ability, the patient may feel uncomfortable, anxious, angry, depressed and/or crave the ability to experience reward and pleasure. However, a patient suffering from any one of those emotions may not necessarily suffer from RDS. Behavior symptoms that an RDS patient may experience include:

1) a depressed mood and/or anhedonia;
2) social anxiety;
3) frequent agitation, aggressiveness and/or explosive temper;
4) easy irritability;
5) low frustration tolerance;
6) Attention Deficit/Hyperactivity Disorder (ADHD) or subsyndromal ADHD that includes inattentive and/or impulsive symptom criteria; and
7) Tourette's syndrome.

The reward-deprived emotional state may result in frequent attempts to experience pleasure, comfort, or relief in ways that may be self-damaging such as danger/thrill-seeking behavior involving life threatening activities, damaging activities or illegal activities; compulsive gambling; binge eating/overeating; addictive behavior (e.g., alcohol, substance use, tobacco use, sexually compulsive behavior); and suicidal ideation and/or attempts. All RDS patients have clinically significant distress or impairment in social, occupational, or other important areas of functioning. However, an individual suffering

from any one of those behavioral symptoms or self-damaging proclivities may not necessarily suffer from RDS.

According to this invention, the methods and compositions provided herein are useful for treating RDS or one or more of the symptoms of RDS in a patient suffering from RDS. Accordingly, the methods of this invention are useful for RDS patients who do not also suffer from any one of the following symptoms selected from the group consisting of: depressed mood and/or anhedonia, social anxiety, frequent agitation, aggressiveness and/or explosive temper, easy irritability, low frustration tolerance, Attention Deficit/Hyperactivity Disorder (ADHD), and subsyndromal ADHD that includes inattentive and/or impulsive symptom criteria, Tourette's syndrome, compulsive or addictive behavior such as substance abuse or sexually compulsive behavior, self-damaging behavior and suicidal ideation.

A patient according to this invention is a human, including children and adults, suffering from RDS.

Any suitable route of administration may be employed for providing the patient with an effective dosage of an MAOB-I of this invention. For example, oral, rectal, parenteral, transdermal, subcutaneous, sublingual, intranasal, intramuscular, intrathecal and the like may be employed as appropriate. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Dosage forms include tablets, scored tablets, coated tablets, caplets, capsules (*e.g.*, hard gelatin

capsules), troches, dragées, dispersions, suspensions, solutions, transdermal patches and the like, including sustained release formulations well known in the art. In one preferred embodiment, the dosage form is a scored tablet or a transdermal patch.

The compositions and separable compositions useful according to this invention include those suitable for oral, rectal, transdermal, sublingual, and parenteral administration (including subcutaneous, intramuscular, intrathecal and intravenous), and transdermal, although the most suitable route in any given case may depend on the patient and the nature and/or severity of the condition being treated. A preferred route of administration according to the methods of the present invention is the oral route or the transdermal route. The composition may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

The compositions or separable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The compositions according to this invention may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

Methods for making transdermal patches including selegiline transdermal patches have been described in the art. [U.S. patent 4,868,218, incorporated by reference herein]

Compositions or separable compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions or separable compositions can be prepared by mixing a compound of this invention with a suitable

non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The magnitude of a prophylactic or therapeutic dose of the active ingredient (*i.e.*, MAOB inhibitor) in the prevention or treatment of a human will vary with the symptoms being exhibited, the severity of the patient's affliction and the route of administration. The dose and dose frequency will also vary according to the age, weight and response of the individual patient. Generally, however, treatment for RDS will be ongoing although the intensity of treatment may vary depending on the patient's condition and exposure to biochemical and environmental stimuli that may warrant a variation on the treatment. In a preferred embodiment, selegiline is given twice a day (bid), in the morning and late afternoon.

The treating physician will know how to increase, decrease or interrupt treatment based upon the patient's response. For example, qualitative determinations of improvement may be assessed by the patient's reports of improved enjoyment or satisfaction

of several ordinary activities such as work, social interaction with friends or family, hobbies and interests.

The various terms described above such as "therapeutically effective amount," are encompassed by the above-described dosage amounts and dose frequency schedule. Generally, a therapeutically effective amount is that amount at which monoamine oxidase B is inhibited but monoamine oxidase A exhibits slight or no reduction in activity in the patient. In one embodiment, the dosage of selegiline is an amount equal to or less than 10mgs per day. In a preferred embodiment, selegiline is administered in an amount less than 10mgs/day. In another embodiment, the dosage of pargyline is less than 30 mgs/day.

Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

EXAMPLE

Patient X is a man in his late 40's who works as a professional. He was in the midst of a divorce from his first and only marriage at the time of his initial visit. He has three children. He presented with depressed mood and suicidal ideation. He described a daily mood pattern of severe depression upon awakening that was severe for about three hours

and became less in the late morning. He would often go to his job about an hour late because of this mood. The rest of the day, his mood was improved but was in the depressive range.

The patient's suicidal ideation was relatively constant and severe, often including plans that were easy to accomplish. He experienced prominent, generalized anxiety. His sleep was not significantly disturbed, though he had much difficulty getting out of bed in the morning because of his low mood and energy.

The patient felt that there was a paucity of pleasure or enjoyment in any aspect of his life. He pursued no interests and was totally preoccupied with his psychiatric syndrome. He carried out his role as father without deriving any pleasure from his interactions with his children.

He alternated between being hostile and aggressive and having feelings of hopelessness and believing that there was no cure or relief from his constant suffering.

His family history included a grandmother who had been hospitalized with depression and a son with panic attacks, agoraphobia and frequent agitated, hostile behavior.

The patient had no history of alcohol or substance abuse. His treatment history over the past 30 years by various physicians includes a wide list of drug treatments. The patient's previous drug treatments are indicated in Table I below.

TABLE I. Prior Treatment History

Drug Administered	Effect
thorazine	N/A
amitriptyline up to 100mg/day	no effect
benzodiazepines	somewhat helpful in calming
fluvoxamine up to 100mg/day	no effect
fluoxetine up to 80mg/day	no effect
valproic acid	no effect
fluoxetine plus desipramine	no effect
lithium up to 900mg/day	patient felt it was not effective; doctor felt there was improvement
venlafaxine up to 375mg/day	no effect
sertraline	no effect
nefazodone up to 100mg/day	no effect
thyroxine	no effect
dextramphetamine at 50-60 mg/day	patient felt it was helpful to get to work; physician thought the patient was "riding the roller coaster of moods"
lithium plus fluoxetine	no effect
bupropion at 75 bid plus moclobemide	patient developed manic behavior

moclobemide plus divalproate plus 4 mg/day clonazepam plus 20mg zolpidem	patient experienced severe disorientation
divalproate up to 500 mg bid	physician thought the patient became hypomanic despite divalproate treatment
lithium up to 1400mg/day plus divalproate at 300mg/day	no effect

Subsequently, patient X came to the applicant for treatment. He was initially treated with lithium up to 900mgs/day together with gabapentin up to 32000mg/day and light therapy. The timing of his worst period of depression was moved back by 30 minutes, but the severity of his depression did not decrease. Melatonin was added to his treatment, but it had no effect. The melatonin treatment was discontinued. Applicant next administered bupropion at 37.5 mg bid. However, the patient became agitated, extremely irritable, and had excessive suicidal ideation. The bupropion treatment was rapidly discontinued. Applicant noted the patients' frequent, chronic complaints about the inability to reach destinations without distraction. The patient was then given 60-80mg/day of methylphenidate (i.e., Ritalin®). The patient experienced improved morning mood (from a depressed to a euthymic state) and experienced new desires. However, during the course of the day, he also experienced rapid and abrupt deteriorations in mood. Further, the positive effects of methylphenidate

treatment decreased after the initial weeks of treatment. Applicant decreased the patient's doses of lithium and gabapentin and then discontinued them. Applicant added clonazepam to the treatment. However, the patient experienced no clinical change. Applicant discontinued administering Ritalin®.

Next, the patient was prescribed selegiline at 2.5mg/day up to two times/day. At 2.5mg/day of selegline, The patient felt a rapid and remarkable response. He described new episodes of enjoying time with his family. He experienced feelings of pride when partaking in a religious holiday with his parents. His chronic suicidal ideation completely stopped. The patient stated that he was experiencing reward in everyday activities and interactions.

When his dosage regimen was increased to 7.5mgs/day dose, the patient experienced increased irritability and a return of previously familiar distressing symptoms. Applicant instructed the patient to return to the 2.5 mgs bid treatment schedule. His current regimen of medications is selegiline at 2.5mgs bid, clonazepam at 0.25 mg bid to tid and melatonin at 12 mgs at bedtime. The clonazepam appears to calm his anxious, "wired" feeling that may either be a side effect of taking selegiline or of an untreated component of his syndrome.

Patient X has begun to develop a new life. He has a new interest in pursuing love relationships, and he pursues many hobbies and activities that he never considered possible in the past. He has begun an exercise regimen and changed his diet to one that is more nutritious and less caloric thereby allowing him to lose weight. He has not experienced any manic,

hypomanic, or agitated behavior during his treatment with selegiline.

At one point, patient X ran out of selegline and went a few days without it. Within a day or so, he experienced a dramatic return of suicidal ideation and previous mood and anxiety symptoms as well as a loss of the pleasure he had been feeling.

The embodiments of the present invention described above are intended to be merely exemplary and those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. All such equivalents are considered to be within the scope of the present invention and are covered by the following claims.

CLAIMS

1. A method for treating reward deficiency syndrome (RDS) in a mammal in need of treatment for RDS comprising the step of administering a therapeutically acceptable amount of a monoamine oxidase B inhibitor (MAOB-I).

2. The method according to claim 1, wherein the mammal is a human.

3. The method according to claim 1, wherein the MAOB-I is selected from the group consisting of selegiline, pargyline, desmethylselegiline, rasagiline, 3-N-phenylacetylamino-2,5-piperidinedione and caroxyazone.

4. The method according to claim 3, wherein selegiline is administered in an amount of 10 mgs or less per day.

5. The method according to claim 3, wherein selegiline is administered in an amount of 5 mgs or less per day.

6. The method according claim 5, wherein selegiline is administered in an amount of 2.5 mgs or less per day.

7. The method according to claim 5, wherein selegiline is administered in an amount of 1 mg or less per day.

8. The method according to any one of claims 1-7, wherein the MAOB-I is administered orally, parentally or transdermally.

9. The method according to any one of claims 1-7, wherein the MAOB-I is administered as a tablet, a capsule or a transdermal patch.

10. A composition comprising less than 2.5 mg of selegiline or a derivative thereof as a single unit or as a unit that is pre-prepared into separable portions, each portion of which comprises less than 2.5 mgs of selegiline.

11. The composition according to claim 10, wherein the single unit or each separable portion comprises less than or equal to 2.0 mgs of selegiline thereof.

12. The composition according to claim 10, wherein the single unit or each separable portion comprises less than or equal to 1.0 mg of selegiline thereof.

13. The composition according to claim 10, further comprising a therapeutic agent.

14. The composition according to claim 13, wherein the therapeutic agent is a benzodiazepine.

15. The composition according to claim 14, wherein the benzodiazepine is selected from the group consisting of chlordiazepoxide, clorazepate, diazepam, flurazepam, halazepam, prazepam, alprazolam,

clonazepam, flunitrazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, and triazolam.

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WO 01/34172 A3

(54) Title: METHODS AND COMPOSITIONS FOR TREATING REWARD DEFICIENCY SYNDROME

(57) Abstract: The present invention relates to methods and compositions for treating Reward Deficiency Syndrome (RDS) using a therapeutically effective amount of a monoamine oxidase B inhibitor. The present invention also relates to compositions for treating RDS comprising selegiline in very low dose.

INTERNATIONAL SEARCH REPORT

'ernational Application No
rCT/US 00/30312

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/135 A61P25/00 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 812 481 A (REISCHIG DIRK ET AL) 14 March 1989 (1989-03-14) column 3, line 18 - line 23 claim 2	10-13
X	US 5 721 258 A (PERGANDE GABRIELA ET AL) 24 February 1998 (1998-02-24) column 5, line 63 - line 65	10-13
A	US 5 550 021 A (BLUM KENNETH ET AL) 27 August 1996 (1996-08-27) the whole document	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 April 2001	11/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Taylor, G.M.

1

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